

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Chin, et al.

Serial No. 10/798,986

Filing Date: 03/12/2004

For: Cell-Based Biosensor For
Harmful Airborne Agents

Examiner: Gitomer, Ralph J.

Art Unit: 1655

AMENDMENT AND
RESPONSE TO OFFICE ACTION

Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

Applicant hereby responds to the Office action dated May 10, 2006.

In the Claims

Please substitute the claims as set forth below in a complete listing. Language added is shown underlined and language deleted is shown in strike through or enclosed in brackets. The amendments include no new matter and are fully supported in the application as filed.

1.(currently amended) A method of monitoring an air atmosphere for a harmful biological or chemical agent, the method comprising:

providing a plurality of mammalian respiratory airway epithelial cells borne on a porous support;

contacting the porous support with a cell nutrient medium and with air by positioning said porous support at an air-liquid interface between the cell nutrient liquid medium and the air;

sampling the air atmosphere to thereby create an air flow over the air-liquid interface so that the respiratory epithelial cells borne on the porous ~~silicone~~ support are contacted by the sampled air; and

monitoring the respiratory epithelial cells for at least one physiological parameter indicating the cells have been exposed to the harmful agent.

2.(currently amended) The method of claim 1, wherein the plurality of mammalian respiratory airway epithelial cells consists of ~~primary~~ rabbit cells.

3.(currently amended) The method of claim 1, further comprising sufficient ~~the cell~~ nutrient medium in contact with at least a lower surface of the porous support to nourish the plurality of respiratory airway epithelial cells.

- 4.(original) The method of claim 1, wherein the porous support comprises silicone.
- 5.(original) The method of claim 1, wherein the porous support comprises a nanoporous silicone composition.
- 6.(original) The method of claim 1, wherein the porous support consists of a nanoporous silicone composition having pores no larger than one micrometer in diameter.
- 7.(currently amended) The method of claim 1, wherein the porous support comprises a silicone composition ~~wherein the~~ having pores consist of a sufficiently small diameter to prevent the plurality of mammalian respiratory airway epithelial cells from ~~falling thereinto~~ entering.
- 8.(original) The method of claim 1, wherein the porous support comprises a nanoporous silicone composition having an average pore size smaller than the average size of the plurality of mammalian respiratory airway epithelial cells.
- 9.(original) The method of claim 1, wherein the plurality of mammalian respiratory airway epithelial cells comprises a confluent layer of cells.
- 10.(original) The method of claim 1, wherein the plurality of mammalian respiratory airway epithelial cells comprises a monolayer of cells.
- 11.(original) The method of claim 1, wherein the plurality of mammalian respiratory airway epithelial cells comprises ciliated cells and goblet cells.

12.(original) The method of claim 1, wherein the plurality of mammalian respiratory airway epithelial cells comprises ciliated cells and goblet cells and the at least one physiological parameter monitored comprises ciliary beating frequency of the ciliated cells.

13.(original) The method of claim 1, wherein the plurality of mammalian respiratory airway epithelial cells comprises ciliated cells and goblet cells and the at least one physiological parameter monitored comprises an electrical response of the plurality of mammalian respiratory airway epithelial cells.

14.(original) The method of claim 1, wherein the plurality of mammalian respiratory airway epithelial cells comprises ciliated cells and goblet cells and the at least one physiological parameter monitored comprises mucin secretion from the goblet cells.

15.(original) The method of claim 1, wherein the harmful biological or chemical agent comprises a toxin.

16.(original) The method of claim 1, wherein the harmful biological or chemical agent comprises a biological warfare agent.

17.(original) The method of claim 1, wherein the harmful biological or chemical agent comprises a chemical warfare agent.

18.(original) A method of monitoring an air atmosphere for a harmful biological or chemical agent, the method comprising:

providing a porous support having an upper surface and a lower surface, and having a plurality of channels etched on the upper surface of the porous support;

contacting the porous support with a cell nutrient medium and with air by positioning said porous support at an interface between the cell nutrient medium and the air so that the lower surface of the support is in contact with the cell nutrient medium and so that the upper surface of the support is in contact with the air;

seeding a plurality of mammalian respiratory airway epithelial cells into the plurality of channels etched on the upper surface of the porous support;

sampling the air atmosphere to thereby create an air flow over the upper surface of the porous support so that the plurality of mammalian respiratory airway epithelial cells seeded into the etched channels are contacted by the sampled air; and

monitoring the plurality of mammalian respiratory airway epithelial cells for at least one physiological change indicating the cells have been exposed to the harmful agent.

19.(original) The method of claim 18, wherein the plurality of mammalian respiratory airway epithelial cells are primary rabbit cells.

20.(original) The method of claim 18, further comprising sufficient cell nutrient medium in contact with a lower surface of the porous support to nourish the airway epithelial cells.

21.(original) The method of claim 18, wherein the porous support comprises silicone.

22.(original) The method of claim 18, wherein the porous support comprises a nanoporous silicone composition.

23.(original) The method of claim 18, wherein the porous support consists of a nanoporous silicone composition having pores no larger than one micrometer in diameter.

24.(original) The method of claim 18, wherein the porous support comprises a silicone composition wherein the pores consist of a sufficiently small diameter to prevent the plurality of mammalian respiratory airway epithelial cells from falling thereinto.

25.(original) The method of claim 18, wherein the porous support comprises a nanoporous silicone composition having an average pore size smaller than the average size of individual cells in the plurality of mammalian respiratory airway epithelial cells.

26.(original) The method of claim 18, wherein the plurality of mammalian respiratory airway epithelial cells comprises a confluent layer of cells.

27.(original) The method of claim 18, wherein the plurality of mammalian respiratory airway epithelial cells comprises a monolayer of cells.

28.(original) The method of claim 18, wherein the plurality of mammalian respiratory airway epithelial cells comprises ciliated cells and goblet cells.

29.(original) The method of claim 18, wherein the plurality of mammalian respiratory airway epithelial cells comprises ciliated cells and goblet cells and the at least one physiological parameter monitored comprises ciliary beating frequency of the ciliated cells.

30.(original) The method of claim 18, wherein the plurality of mammalian respiratory airway epithelial cells comprises ciliated cells and goblet cells and the at least one physiological parameter monitored comprises an electrical response of the plurality of mammalian respiratory airway epithelial cells.

31.(original) The method of claim 18, wherein the plurality of mammalian respiratory airway epithelial cells comprises ciliated cells and goblet cells and the at least one physiological parameter monitored comprises mucin secretion from the goblet cells.

32.(original) The method of claim 18, wherein the harmful biological or chemical agent comprises a toxin.

33.(original) The method of claim 18, wherein the harmful biological or chemical agent comprises a biological warfare agent.

34.(original) The method of claim 18, wherein the harmful biological or chemical agent comprises a chemical warfare agent.

Remarks

Applicant appreciates the Examiner's careful review of the application and submits the following remarks in support of the patentability of the pending claims.

Concerns Under Section 112 Have Been Addressed

The language inconsistencies noted by the Examiner in claims 1, 2, 3 and 7 have been corrected. Additionally, counsel corrected claim 13, which was originally missing a period at the end of the sentence. Since these concerns have been addressed, Applicants respectfully request withdrawal of the rejections under Section 112.

The Cited Reference By Zhong et al. Is Non-Analogous Art

Applicants believe that the cited reference by Zhong et al. represents non-analogous art and, consequently, must present this argument in a timely manner or the reference could be considered to be admitted by Applicants.

The scope of analogous art, according to Judge Randall Rader, turns on: (1) whether the art is from the same "field of endeavor," regardless of the problem addressed; and, (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is "reasonably pertinent" to the particular problem with which the inventor is involved. The identification of analogous prior art is a factual question reviewable for substantial evidence, he added. In re Bigio, 381 F.3d 1320 (Fed. Cir., 2004), 72 USPQ2d 1209.

The test requires the PTO to determine the appropriate field of endeavor from explanations of the invention's subject matter in the patent application, the court explained, including the embodiments, function, and structure of the claimed invention. The assessment of the

field of endeavor is not a wholly subjective call, Judge Rader observed, since there must be a basis in the application for limiting or expanding the scope of the field of endeavor.

Regarding the cited reference by Zhong et al., the field of endeavor is given by these inventors at column 2, line 40, wherein they state as follows.

The objectives of the present invention include providing a silicone resin which is soluble in organic solvents such as toluene, has a useable solution shelf-life, and *which is suitable for forming crack-free electrically insulating films on electronic devices*. Another objective is to provide a silicone resin composition which after coating on a substrate can be heated to form a microporous film have a narrow pore size distribution and a low dielectric constant. *Such low-dielectric constant films can be formed on electrical components such as semiconductor devices by conventional methods to form microporous crack-free films having a dielectric constant less than about 2.*

Emphasis has been added, however, from the above it would seem clear that the invention by Zhong et al. is directed to the field of semiconductors and is completely unrelated to biotechnology and substrates for cell culture, as the present invention.

Since the Zhong et al. reference is not within the field of the inventor's endeavor, it may still be considered if the reference still is "reasonably pertinent" to the particular problem with which the inventor is involved. In the present application the inventors attempt to provide a method for air sampling for toxic substances, such as during chemical warfare or acts of terrorism. In the Zhong et al. reference the inventors attempt to find a solution for the problems inherent in present semiconductors. "Semiconductor devices often have one or more arrays of patterned interconnect levels that serve to electrically couple the individual circuit elements forming an integrated circuit (IC). These interconnect levels are typically separated by an insulating or dielectric film. Previously, a silicon oxide

film formed using chemical vapor deposition (CVD) or plasma enhanced techniques (PECVD) was the most commonly used material for such dielectric films. However, as the size of circuit elements and the spaces between such elements decreases, the relatively high dielectric constant of such silicon oxide films is inadequate to provide adequate electrical insulation." See Zhong et al. at column 1, lines 10-21.

Accordingly, the reference by Zhong et al. is neither in the same field of endeavor as the present application, nor does it attempt to solve the same or even a similar problem. For those reasons, Applicants believe the Zhong et al. reference fits the requirements for non-analogous art and respectfully assert that this reference does not provide permissible support for a *prima facie* case of obviousness against the pending claims. Applicants, therefore, respectfully request that this reference be deemed non-analogous art and be withdrawn.

The Claimed Invention Is Nonobvious Over The Remaining References

The Examiner has also cited the references by S. Romet-Haddad et al. and by Marano and Volochine as rendering the present invention obvious and unpatentable under Section 103(a). For the following reasons, Applicants respectfully disagree.

The Romet-Haddad et al. reference is a scientific article published in *Cell Biology and Toxicology*, Vol. 8, No. 3, pp. 141-150, 1992. The title of this article is "Tracheal Epithelium In Culture: A Model For Toxicity Testing of Inhaled Molecules." *Cell Biology and Toxicology* appears to be a peer-reviewed journal.

The cited reference by Marano and Volochine (NTIS PB 91110841) is a reference written in French and is titled Activity Report under Contract DRET n° 87/174. DRET stands for *Direction des Recherches Etudes et Techniques*, which appears to be a division of a French government agency, Délégation Générale pour l'Armement (General

Delegation for Armaments). Professor Marano is also a co-author in the Romet-Haddad et al. cited reference, however, this reference appears to be a progress report made to the French government under the identified contract grant. All the experimental procedures described in this reference, Marano and Volochine, are the same as those described in the Romet-Haddad et al. reference. In other words, the two cited references are essentially the same material; this assertion is based on undersigned counsel's ability to read the document in its original French.

With regard to the Romet-Haddad et al. reference, under the paragraph captioned "Cell Culture Methods" on page 142, the authors state that "these explants were grown in collagen-gel coated dishes and covered with minimum essential medium (MEM) as previously described (Baeza *et al.*, 1991)." Accordingly, the cultured tissue of tracheal epithelial cells was grown *covered* in a liquid medium and not at an air-liquid interphase. The same method is described at the bottom the first page of the NTIS PB 91110841 document, under Section I.1 - Méthod d'obtention, last sentence on this page: "They were deposited in Petri dishes, with the luminal zone underneath, on a support of collagen gel supplemented with nutritive elements and were *covered* 1 hour following deposition with 200 µl of MEM medium containing 10% fetal calf serum . . ." Emphasis added. Clearly, the experimental procedures detailed in both these references call for the cells to be covered by liquid medium.

Moreover, Applicants point out that on page 142 under the paragraph captioned "Chemical Treatments" Romet-Haddad *et al.* provide directions for preparing stock solutions of acrolein and mechlorethamin, the chemicals to be tested for toxic effects on the cultured tracheal epithelial cells. Regarding the chemical toxicity tests the authors state "for all experiments, each of the chemical concentrations was systematically tested on three cultures." Under the paragraph captioned "Viability Assays," also on page 142 of the

cited reference, the authors state that "chemicals were applied in a single dose and in various concentrations on day 7 and viability measurements were carried out after 24h of treatment." In the NTIS PB 91110841 reference, where the top of the page is captioned "Etude De La Toxicite De Quatre . . ." (unfortunately, the pages are not numbered in this document), under section I "Mise en solution des produits" - it describes that the same procedure is used for each toxic tested ("Le même protocole a été adopté pour chaque toxique testé."). Directly following, in subsection 1, it states (on the following page) that solutions of the products were prepared in the same culture medium supplemented with growth factors ("Les solutions de produits sont préparées dans le milieu de culture supplémente en facteurs de croissance . . .").

Applicants believe it is clear that Romet-Haddad et al. cultured their tracheal epithelial cells covered in medium and applied chemicals at various concentrations in a liquid form to these cell cultures. Neither cited reference grew the tracheal epithelial cells at an air-liquid interphase, and neither reference suggests doing so. Additionally, the experimental methodology in both references calls for the chemicals being tested for toxicity to be applied in liquid form to the cell cultures. There is no suggestion of exposing the cultured cells to an air flow containing the suspect chemicals. Furthermore, in the Romet-Haddad et al. system, the cultured cells could not be exposed to airborne chemicals, since the cells are grown *covered* in medium.

For those reasons, Applicants believe that the combination of cited references does not render the claimed invention obvious. Applicants, therefore, respectfully request that the obviousness rejection under Section 103(a) be withdrawn.

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Conclusion

For the reasons set forth above, Applicant believes the pending claims are patentable over the cited art and respectfully requests that the Examiner allow the application.

If further prosecution may be aided by a conference, Applicant respectfully requests that counsel be contacted by telephone at the Examiner's convenience.

Respectfully submitted,



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